



Should Calcitonin Be Measured in Every Thyroid Nodule?

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Mine Adaş and Gökhan Adaş

Abstract

There are controversial suggestions in the literature about the routine measurement of calcitonin (Ct) in thyroid nodules. Barriers in front of measuring routine serum calcitonin are cost-effectiveness and the possibility of having elevated serum Ct in the absence of medullary thyroid carcinoma (MTC). Here we report a sporadic MTC patient with negative fine needle aspiration biopsy (FNAB) result whose diagnosis was made by preoperative calcitonin measurement. As we perform routine Ct measurement before surgery, the surgeon becomes aware of the MTC earlier, and this gives the opportunity of making an appropriate surgical procedure which is crucial for patients' outcome.

grade 1b palpable thyroid gland with 1 cm nodules on both lobes. Other physical examination findings and family history were unremarkable. Thyroid function tests were within the normal limit. Anti-TPO was 117.6 IU/ml (<9 IU/ml). Neck ultrasound (USG) revealed bilateral hypoechoic thyroid nodules with irregular margins and microcalcifications. Fine needle aspiration biopsy (FNAB) from left-sided nodule was benign, while right-sided nodule showed Hurthle cell metaplasia with benign findings. We measured calcitonin (Ct) according to our routine practice. The serum calcitonin level was 4049 pg/ml (0–11.5 pg/ml). Repeated Ct level at another center was >1636 pg/ml (<10 pg/ml) again. Twenty-four-hour urine estimation of catecholamines, normetanephrine and plasma normetanephrine, serum calcium, and parathyroid hormone (PTH) was determined to identify or exclude pheochromocytoma and hyperparathyroidism. All were within the normal limits. RET protooncogene testing was negative. The patient underwent total thyroidectomy and central compartment node clearance (level VI). Postoperative histopathology confirmed thyroid medullary carcinoma of 1.2 cm in the right lobe, papillary microcarcinoma of 0.5 cm at three different foci at the left lobe, and metastatic medullary thyroid carcinoma in the resected lymph nodes. After thyroid operation serum Ct level was 10.3 pg/ml (0–11.5 pg/ml).

14.1 Case Presentation

A 45-year-old woman admitted to endocrinology outpatient clinic with a 4-week history of palpable cervical mass. Physical examination revealed

M. Adaş (✉)
University of Health Sciences (SBÜ), Okmeydanı
Training and Research Hospital, Istanbul, Turkey

G. Adaş
University of Health Sciences (SBÜ), Haseki
Training and Research Hospital, Istanbul, Turkey

14.2 Discussion

14.2.1 Evaluation and Diagnosis

The rate of MTC diagnosed only after thyroid operation is approximately 10–15% [1]. This delay in diagnosis can adversely affect the patient's outcome. Initial surgery is an important modality in the treatment and course of MTC. Diagnosis of MTC before surgery also has significance for the diagnosis of MEN syndromes especially accompanying life-threatening pheochromocytoma in index cases. There are controversial suggestions in the literature about the routine measurement of Ct in thyroid nodules. "The American Thyroid Association (ATA) Guideline for Thyroid Nodule and Differentiated Thyroid Cancer" does not recommend either for or against routine measurement of serum Ct (Recommendation 4) [2], while "The American Association of Clinical Endocrinologists (AACE), Associazione Medici Endocrinologi (AME), and European Thyroid Association (ETA) Thyroid Nodule Guidelines" recommend measurement of basal serum Ct level as a useful test in the initial evaluation of thyroid nodules [3]. The reasons for ATA recommendation are unresolved issues of assay performance, lack of pentagastrin availability in the United States, and potential biases in the cost-effectivity analysis [2]. The ATA recommendation and evidence quality about Ct are insufficient. There are false-negative and false-positive results of basal Ct measurement that cause misdiagnosis. Technical problems, (hook effect, heterophilic antibodies), some drugs (omeprazole), chronic renal failure, pernicious anemia, and lymphocytic thyroiditis are some reasons of false-positive results, while nonsecretory medullary thyroid carcinoma is the false-negative result [4]. If basal calcitonin level is increased, the test should be repeated, and if confirmed in the absence of modifiers, a pentagastrin or calcium stimulation test will increase the diagnostic accuracy [3]. However, pentagastrin is not available in every country, and there are problems with calcium stimulation test like cutoff levels, cost, assay performance, sensitivity, and specificity [2]. The main rationale for the rec-

ommendation of AACE, AME, and ETA concerning Ct measurement in the thyroid nodule is its higher sensitivity compared to FNAB [5–11]. As it is in our case, FNAB was not able to diagnose the MTC of the patient. If routine calcitonin had not been measured, the patient could be misdiagnosed.

Another problem in the routine measurement of basal calcitonin for every thyroid nodule is the cost-effectiveness of this screening. There are studies from the United States and European countries demonstrating that it is valuable to measure calcitonin level [12–14]. However, the costs of finding one patient with abnormal results and MTC are quite reasonable for routine basal Ct measurement, compared with the potential costs of missing the diagnosis of this treatable malignant condition [15].

14.2.2 Management

One of the important benefits of knowing preoperative Ct is the tailoring of surgical treatment. Central neck lymph node dissection is an important and necessary treatment modality in the management of MTC. As we perform routine Ct measurement before surgery, the surgeon becomes aware of the MTC earlier, and the procedure is at least total thyroidectomy and central neck lymph node dissection as it was in our case. Also, preoperative Ct measurement is effective in the detection of clinically occult MTC [5–8]. In addition, screening thyroid nodules with serum Ct measurement allows the diagnosis and treatment of MTC at an earlier stage, resulting in a better outcome compared with MTC not detected by serum Ct measurement [13].

14.3 Follow-Up and Outcome

The patient has been under follow-up for 6 years. Her postoperative serum calcitonin level was 10.3 pg/ml (0–11.5 pg/ml). After 5 years of follow-up, last serum calcitonin level was 13.56 pg/ml (0–6.4 pg/ml). Neck USG revealed nothing pathologic. The patient is on L-thyroxin replacement therapy.

14.3.1 The Future

Barriers in front of measuring routine serum Ct are cost-effectiveness and the possibility of having elevated serum Ct in the absence of an MTC. Other different diagnostic modalities can help us in this regard. Recent small studies have shown improved sensitivity with Ct measurement in FNA washout fluid with as high as 100% accuracy [16]. Procalcitonin, the precursor of Ct, has been reported as a potential MTC marker and could be a good candidate for a first-line screening test to exclude MTC in patients with suspicious thyroid nodules [17].

What Can We Learn from This Case?

- Ct measurement is an effective method for the diagnosis of MTC and is superior to FNAB concerning diagnosis of MTC.
- Recognition of MTC by preoperative calcitonin measurement increases the chance of curative therapy by diagnosing MTC in the early stages and then performing the appropriate surgical procedure.

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